D3 cont

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.8% to about 15% of the first component, and wherein the disease is atopic dermatitis, asthma, urticaria, rhinitis, uveitis, type II diabetes, cystic fibrosis, colitis, or hepatic fibrosis.

## REMARKS

Claims 12-17, 20-26, and 29, are currently pending in this application and have all been rejected by the Examiner. With this response, claims 12, 20, and 26, have been amended; and claims 13-14 have been canceled. Applicants submit that all of the claims are in condition for allowance and request reconsideration.

**Obviousness Rejection**

The Examiner rejected claims 12-17, 20-26, and 29, under 35 U.S.C. § 103(a), as allegedly being unpatentable over Bartlett, *et al* (U.S. Patent No. 4,965,276). *Office Action*, page 2. According to the Examiner, Bartlett "embraces a pharmaceutical composition that comprises both compounds 1 and 2 as components of a single composition." *Id.* Bartlett, however, does not disclose the full range of concentrations recited for compounds 1 and 2 in the claims. In this regard, the Examiner notes that presently claimed compound 2 may have a concentration as high as 50% of compound 1. *Office Action*, pages 2-3. Thus, when compound 1 is 20 mg, compound 2 may be present in the composition at 10 mg (50%). This, the Examiner believes, is high enough to encompass the range of concentrations described by Bartlett. Thus, the Examiner concludes that the claims are obvious over Bartlett.

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To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings in the manner proposed by the Examiner. See M.P.E.P. § 2143. The suggestion or motivation must be found in the prior art, not in Applicant's disclosure. See *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Moreover, the suggestion to combine or modify the prior art teachings must be clear and particular. *See In re Dembiczak,* 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999).

Applicants contend that the Examiner has failed to establish a *prima facie* case of obviousness. There simply is no suggestion in the prior art to modify the teachings of Bartlett in a manner that would lead one of skill in the art to employ the concentrations of compounds 1 and 2 recited in the presently amended claims.

The presently amended claims are directed to combinations of compounds 1 and 2, wherein compound 2 is present at a concentration of about 0.8 to about 15% of the concentration of compound 1. Thus, the maximum concentration of compound 2 (when compound 1 is 20 mg) is about 3 mg. The prior art does not teach any compositions containing concentrations of compounds 1 and 2 that are even remotely close to these amounts. Rather, Bartlett describes the activity of compounds 1 or 2 when used separately at significantly higher concentrations than those recited in the present claims.

For example, in Table 1, Bartlett discloses that 5 and 10 mg/kg of compound 1 have almost zero effect (less than 5%). In fact, 28 mg/kg of compound 1 were required to achieve any appreciable biological effect. In Table 2, both 5 and 10 mg/kg of compound 1 again show less than a 5% effect. It required 20 or 28 mg/kg of compound

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1 to achieve any appreciable level of activity. Table 3 similarly indicates that compound 1 only works at concentrations of 20 mg/kg or higher. With respect to compound 2, Bartlett teaches that it is only effective at concentrations of 20 or 30 mg/kg (See Table 2). No lower concentrations of compound 2 are ever described. Moreover, no combinations of compound 1 and 2 are tested. This would lead one of skill in the art to use higher amounts of compounds 1 or 2 to achieve an effective result. There is no suggestion to use lower amounts, as claimed by Applicants. Quite the opposite, Bartlett teaches that the lower amounts do not work.

The present specification makes note of these deficiencies in the prior art. Specifically, on page 1, lines 15-27, Applicants discuss a related European counterpart to this application (EP 0217206), which provides an identical version of Bartlett's tables 2 and 3. With respect to this data, the specification states that "the oral administration of 5 mg or 10 mg of compound 1 or compound 2, in each case on its own, per kg, does not have any significant effect." *Specification*, page 1, lines 25-27.

Given only the teachings of Bartlett, one of skill in the art would not be guided to employ small amounts of compound 2 (0.8% to 15% of the concentration of compound 1, as claimed by Applicants) in combination with compound 1. Furthermore, the Examiner has not pointed to any other motivation that would lead one of ordinary skill to modify Bartlett and to obtain the claimed invention. Therefore, without some other teaching, the presently amended claims are not obvious in view of Bartlett. Applicants respectfully request that the rejection be withdrawn.

Applicants further contend that even if a prima facie case of obviousness were established, which has not been done here, the rejection would be rebutted by the

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evidence of unexpected results that has already been made of record. *See, e.g., Preliminary Amendment*, dated April 2, 2001. In those arguments, Applicants demonstrated that the combination of compound 1 with a small amount of compound 2 yields a synergistic activity that is totally unexpected. Applicants note that the claims are now entirely commensurate in scope with the concentrations for which synergy has been clearly demonstrated (see, e.g., Specification, Table 1). And, as the Examiner has noted in the Office Action, Bartlett does not teach or suggest any synergism from the combination of compounds 1 and 2, especially at the lower amounts claimed by Applicants. In fact, Bartlett suggests that such amounts of compound 2 would not work at all. Thus, once again, the claims are unobvious in view of Bartlett.

**Conclusion**

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing pending claims 12-17, 20-26, and 29, in condition for allowance. Therefore, this Amendment should allow for immediate action by the Examiner. Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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GARRETT & DUNNER, L.L.P.

Dated: February 12, 2002

By: _____
M. Todd Rands
Reg. No. 46,249

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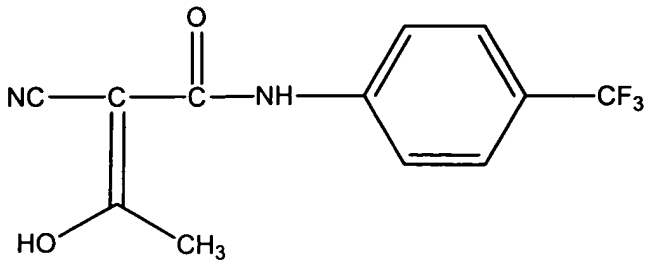
## APPENDIX

12. (Amended) A solid composition comprising:

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I




(I)

or a stereoisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about [0.3%] 0.8% to about [50%] 15% of the first component.

20. (Amended) A method of treating an immunological disease comprising administering to a patient in need of such treatment, a therapeutically effective amount of a solid composition comprising

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I

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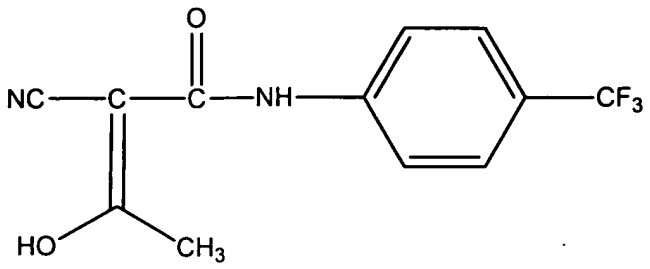


or a sterioisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

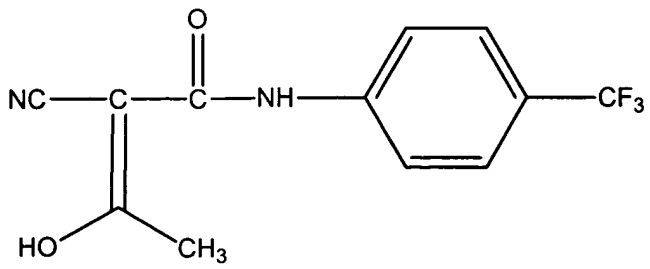
a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about [0.3%] 0.8% to about [50%] 15% of the first component.

26. (Amended) A method of treating a disease comprising administering to a patient in need of such treatment, a therapeutically effective amount of a solid composition comprising

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I



or a sterioisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I;and

a third component comprising a pharmaceutically tolerated excipient;

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wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about [0.3%] 0.8% to about [50%] 15% of the first component, and wherein the disease is atopic dermatitis, asthma, urticaria, rhinitis, uveitis, type II diabetes, cystic fibrosis, colitis, or hepatic fibrosis.

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